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Safe and fast tetrazole formation in ionic liquids

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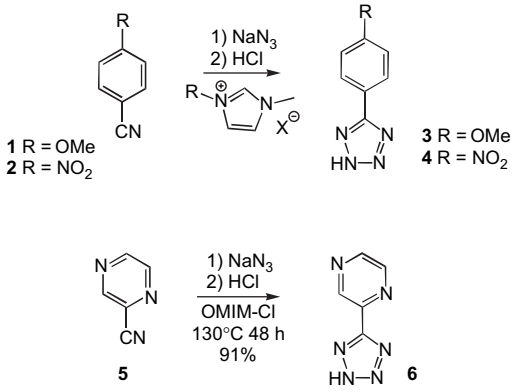
Abstract—The [2+3] cycloaddition of nitriles and azides is reliable for intramolecular reactions, but the hazards with volatile azides in intermolecular reactions are tremendous. Zinc catalysis in aqueous solution is a magnificent improvement, but requires the removal of the zinc salts from the acidic product. Herein, we report safe solvents featuring low vapor pressure and good solubility of NaN_3. Ionic liquids based on alkylated imidazoles combined with microwave heating turned out to be a solution for the given tasks.

1. Introduction

1*H*- and 2*H*-Tetrazoles are regarded as isosteric replacements[1] of carboxylic acids with improved properties in drug metabolism and pharmacokinetics. Thus, they are frequently employed in the lead optimization of ethical drug candidates to enhance the oral bioavailability. Several successful examples of this strategy are present in the sartane drug family, which is used to treat hypertension.[2,3] The [2+3] cycloaddition of nitriles and azides is a reliable method for intramolecular cases, but volatile azides create tremendous hazards in intermolecular reactions. Large-scale processes solve some of the safety issues by using non-volatile tin azides, but introduce the problem of tin recovery.[4,5] The 'click' chemistry approach utilizing[6] zinc catalysis in aqueous solution is a magnificent improvement over previous methods, but sometimes still requires the tedious removal of zinc salts from the acidic products. Moreover, the reaction rates at 100 °C are often insufficient for bulk intermediates. The economic 'click' processes in water require higher temperatures and pressurized vessels. The classical approach utilizes sodium azide and trialkylamines in refluxing toluene, but is limited to the laboratory scale because of volatile ammonium azides, which are prone to sublimation. Furthermore, toluene is not a good solvent for NaN_3, which results in slow turnover, azide deposits and has thus to be regarded as an unsafe, poor alternative. The solvent free conversion by tetrabutylammonium fluoride and trimethyl azide[7] is very attractive for small-scale experiments, but the exothermic azide formation will be hard to control in upscaled reactions.[8] We set out to investigate safer solvents featuring a low vapor pressure and good solubility of NaN_3 and compared them to the methods published by Amantini,[7] Sharpless[6] and Hallberg.[9] Commercial ionic liquids[10,11] (IL) based on alkylated imidazoles turned out to be a versatile solution for the given tasks. Two nitriles (**1** and **2**, Scheme 1) were selected to explore the influence of the methylimidazolium substituents: methyl, butyl, hexyl and octyl. It turned out that these substituents have only minor impact on the outcome of the reaction (Table 1, entries 6–8)[12] in comparison to the contribution of the acid/azide ratio. But there is hidden value in these alkyl chains. The more lipophilic hexyl and octyl imidazoles are less miscible with water and allow easier aqueous extraction of the products, which simplifies the product isolation and improves the isolated yields. The counter anion of the ionic liquids was varied from: Cl^-, Br^-, $^-SO_3CF_3$ to $^-PF_3(C_2CF_5)_3$ and have a higher impact. There was no general trend observed for the two halides, but the halides are far better than triflate or the perfluorinated phosphate (Table 1, entries 28 and 29). The ionic liquids



Scheme 1. Tetrazole formation from commercial nitriles.

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Table 1. Tetrazole formation in different ionic liquids at varying temperatures and stoichiometric ratios

Entry	Substrate or product	NaN_3 (equiv)	HOAc (equiv)	Ionic liquid	*T*/time	Turnover (%)	Yield (%)
1	4-Methoxybenzonitrile (**1**)	1.1	1.5	[BMIM]Br	70 °C/38 h	62	17
2	4-Methoxybenzonitrile (**1**)	1.1	1.5	[BMIM]Cl	70 °C/38 h	28	43
3	4-Methoxybenzonitrile (**1**)	2.2	1.5	[HMIM]Cl	70 °C/38 h	87	56
4	4-Methoxybenzonitrile (**1**)	1.1	1.5	[OMIM]Cl	70 °C/38 h	79	76
5	4-Methoxybenzonitrile (**1**)	1.1	1.5	[BMIM]Br	170 °C/24 h	98	94
6	4-Methoxybenzonitrile (**1**)	1.1	1.5	[BMIM]Cl	170 °C/24 h	89	82
7	4-Methoxybenzonitrile (**1**)	1.1	1.5	[HMIM]Cl	170 °C/24 h	95	91
8	4-Methoxybenzonitrile (**1**)	1.1	1.5	[OMIM]Cl	170 °C/24 h	97	94
9	4-Methoxybenzonitrile (**1**)	1.1	0.7	[OMIM]Cl	170 °C/24 h	98	98
10	4-Nitrobenzonitrile (**2**)	1.1	1.5	[BMIM]Br	70 °C/72 h	97	91
11	4-Nitrobenzonitrile (**2**)	1.1	1.5	[MMIM]Cl	70 °C/72 h	94	89
12	4-Nitrobenzonitrile (**2**)	1.1	1.5	[HMIM]Cl	70 °C/72 h	72	60
13	4-Nitrobenzonitrile (**2**)	1.1	1.5	[OMIM]Cl	70 °C/72 h	97	89
14	2-Pyrazylcarbonitrile (**5**)	2	0.5	[OMIM]Cl	130 °C/48 h	>95	91
15	4′-Methyl-2-biphenylcarbonitrile (**7**)	2	0.5	[MMIM]Cl	140 °C/48 h	93	78
16	4′-Methyl-2-biphenylcarbonitrile (**7**)	1.1	1.5	[BMIM]Br	170 °C/48 h	70	12
17	4′-Methyl-2-biphenylcarbonitrile (**7**)	1.1	1.5	[BMIM]Cl	170 °C/48 h	62	1
18	4′-methyl-2-biphenylcarbonitrile (**7**)	1.1	1.5	[HMIM]Cl	170 °C/48 h	71	35
19	4′-Methyl-2-biphenylcarbonitrile (**7**) (10 mmol)	1.1	1.5	[OMIM]Cl	170 °C/48 h	>95	71
20	4′-Methyl-2-biphenylcarbonitrile (**7**)	2	0.5	[OMIM]Cl	170 °C/24 h	100	59
21	4′-Methyl-2-biphenylcarbonitrile (**7**)	3	0.7	[BMIM]Cl	200 W/1 h	85	80
22	4′-Methyl-2-biphenylcarbonitrile (**7**)	2	0.2	[OMIM]Cl	170 °C/24 h	44	18
23	**8** (0.75 mmol)	3	0.7	[BMIM]Cl	140 °C/8 h	66	57
24	**8** (0.75 mmol)	3	0.7	[BMIM]Cl	140 °C/15 h	91	77
25	**8** (0.75 mmol)	3	0.7	[BMIM]Cl	140 °C/24 h	100	73
26	**8** (0.75 mmol)	3	0.7	[BMIM]Br	140 °C/24 h	100	48
27	**8** (0.75 mmol)	3	0.7	[HMIM]Cl	140 °C/24 h	85	73
28	**8** (0.75 mmol)	3	0.7	$[BMIM]SO_3CF_3$	140 °C/24 h	26	6
29	**8** (0.75 mmol)	3	0.7	$[HMIM]PF_3(C_2F_5)_3$	140 °C/24 h	0	0
30	**9**	3	1	[BMIM]Cl	170/0.5 h, mw	100	89[a]
31	**7**	3	1	[BMIM]Cl	170/0.5 h, mw	58	40[a]
32	**10**	3	1	[BMIM]Cl	170/0.5 h, mw	100	97[a]
33	**5**	3	1	[BMIM]Cl	170/0.5 h, mw	90	77[a]
34	**11**	3	1	[BMIM]Cl	170/0.5 h, mw	n.d.	26[a]
35	**8**	3	1	[BMIM]Cl	170/0.5 h, mw	100	88[a]

[BMIM]: 1-butyl-3-methylimidazolium, [MMIM]: 1-methyl-3-methylimidazolium, [HMIM]: 1-hexyl-3-methylimidazolium, [OMIM]: 1-octyl-3-methylimidazolium. Concn: 0.5 M sample size 1 mL, if not noted otherwise. The turnover was controlled against internal stand, the optimized yields are isolated yields, mw=Biotage® Initiator™ microwave.

[a] Crude yields determined by HPLC.

based on *N*-sulfonamide anions display sufficient vapor pressure to allow distillation.[13] Thus, they were excluded from our investigation.

Initially, the temperature range had to be optimized to guarantee complete conversion within 24 h. This was achieved at 70 °C with electron deficient substrates such as **2**, which is known to react readily during azide formation.[6,8] The less electron deficient pyrazine-2-carbonitrile **5** demanded a higher temperature (130 °C) and extended reaction time of 48 h. The electron rich substrates such as **1** and **8** required even higher reaction temperatures of 170 and 140 °C, respectively. Extended reaction time or higher reaction temperatures resulted in decreased yields for all tetrazoles. This was due to both product and solvent decompositions. A crucial role was assigned to the amount of acetic acid added. Large excess of HOAc versus NaN_3 drove the volatile HN_3 out of the reaction mixtures and thus created a safety issue. Equimolar or substoichiometric amount of acetic acid in relation to sodium azide provided good yields, sufficient reaction rates and economic utilization of NaN_3.

The experiments summarized in Figure 1 provided the standard procedure (140 °C, 0.5 mmol, 24 h in a screw capped 1 mL vial, 3 equiv NaN_3, 1 equiv acid in 100 mg IL) in IL for comparison against the established methods from Amantini and Sharpless.[6,7] All compounds were isolated after aqueous work up, extraction by ethyl acetate or precipitation, where appropriate. The synthesis in IL turned out to be superior in isolated yield for 13 out of 20 products. Amantini method provided the other seven products, e.g., **9** and **23** (Fig. 1), in better yields. However, this method requires a hazardous combination of reagents. The Sharpless method was sometimes even, but generally lacked in isolated yield. The difficulty in isolation of water soluble products (clog $P<1$) was a major cause for the poor yields of the compounds **11**, **24**–**26** (Fig. 1 and Scheme 2). We selected two advanced intermediates (**7**+**8**, Scheme 3) from the synthesis of sartane drugs[2,3] to explore the applicability to functionalized substrates. The commercial biphenylnitrile **7** required an elevated reaction temperature and careful optimization of the stoichiometry to result in **14** with a yield of 78%. However, the necessary reaction time was rather long, which resulted in significant byproduct formation, mainly through product decomposition. However, the tetrazole formation can be accelerated by microwave heating of DMF solutions.[9] The desired rapid heating was reported for $[BMIM]PF_6$. The standard alkyl-[MIM] based ionic liquids do not feature dipole moments suitable for rapid microwave heating, thus the energy absorption is due to ionic conductivity.[14,15]

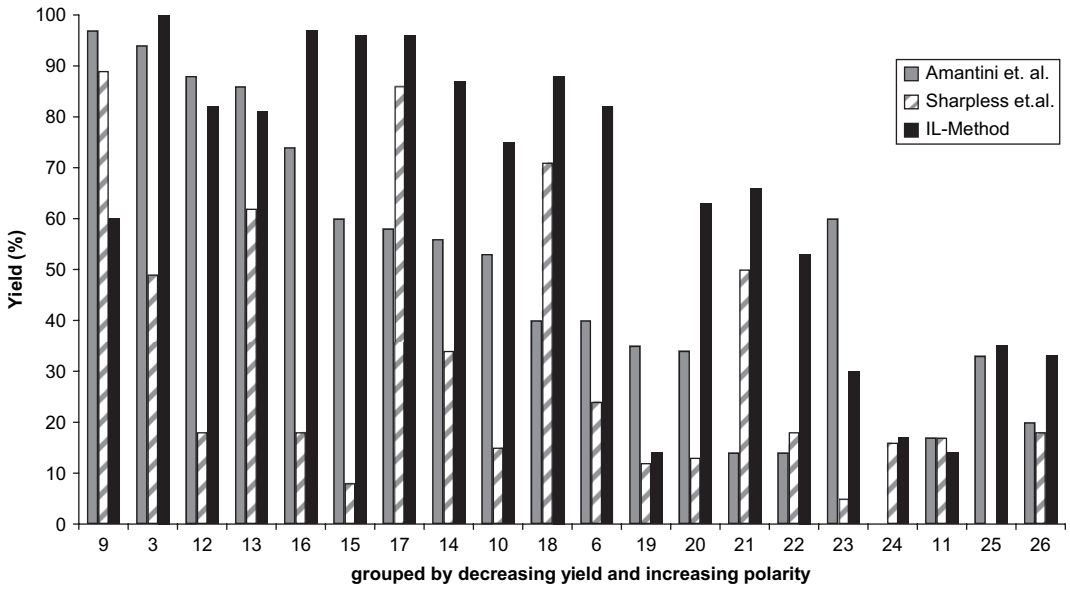
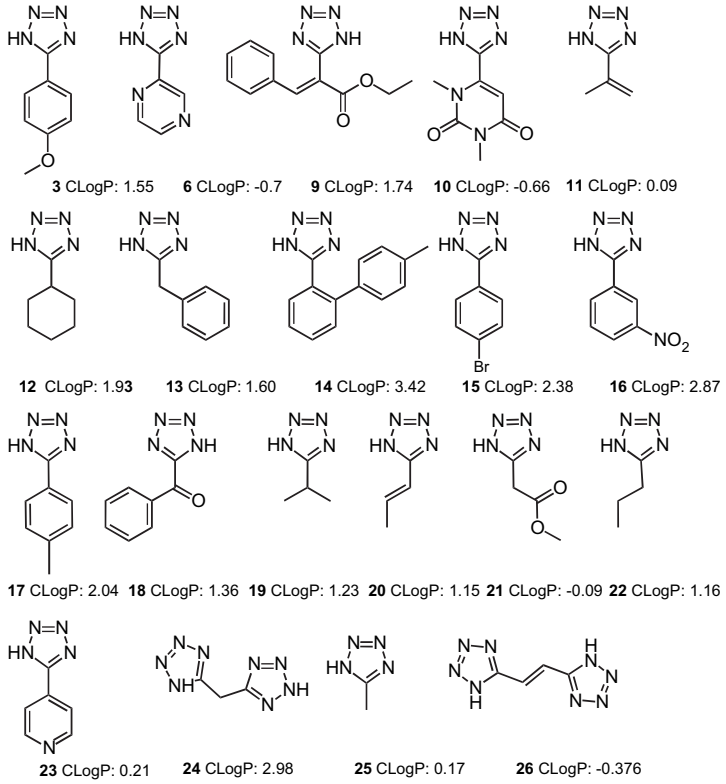


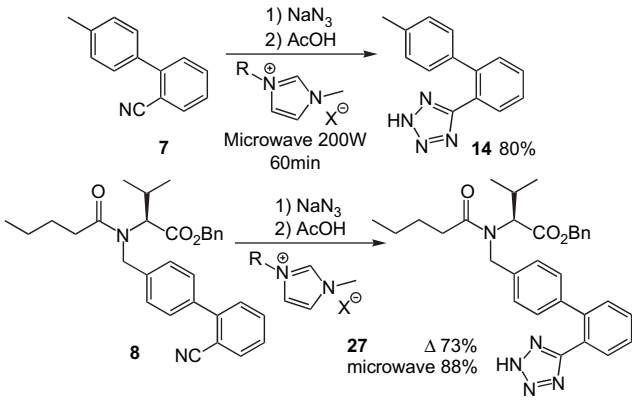
Figure 1. Comparative tetrazole synthesis (Scheme 2 for structure). IL-method: 140 °C, 24 h.

Therefore, we investigated the heat rate of the selected pure IL in comparison to pure DMF under otherwise identical conditions to select suitable candidates. Up to 250 W of microwave irradiation was required to achieve a similar temperature profile as for DMF (Fig. 2).[9] The depicted [BMIM]Cl displayed an induction phase for the energy absorption and ionic conductivity, which increased significantly above 60 °C. Thus, it is due to the melting and the onset of ionic conductivity. A similar effect was observed for [BMIM]Br and [HMIM]Cl. Preliminary investigations of the three ILs by differential scanning calorimetry did not reveal any phase transitions or decomposition between −100 and 200 °C, except for the melting points of [BMIM]Cl at 41 °C (Fig. 3) and [BMIM]Br at 77 °C. The ILs were stable for one heat cycle as judged by ^{1}H NMR spectroscopic analysis. However, repeated heating (3×) resulted in partial decomposition (15%) as judged by ^{1}H NMR spectroscopy. This thermal decomposition has been reported previously.[16,17]

Regardless of the IL decomposition, the reaction time was dramatically shortened using microwave heating at 200 W



Scheme 2. Tetrazole formation from commercial nitriles.



Scheme 3. Synthesis of advanced sartane intermediates.

setting in a burst sealed reaction vessel (entry 21). No attempts were initially made to control the temperature at the small scale of the reaction (0.75 mmol) in a household microwave oven. The microwave heated reaction was complete within 60 min and far more selective (compare entries 15–22). It furnished the product in 80% yield. The more detailed investigation was conducted in a Biotage Initiator™, which allowed to monitor the pressure and temperature over time. The ILs were screened for rapid heating, which in some cases varied significantly due to water impurities. Several ILs displayed the desired rapid heating and were,

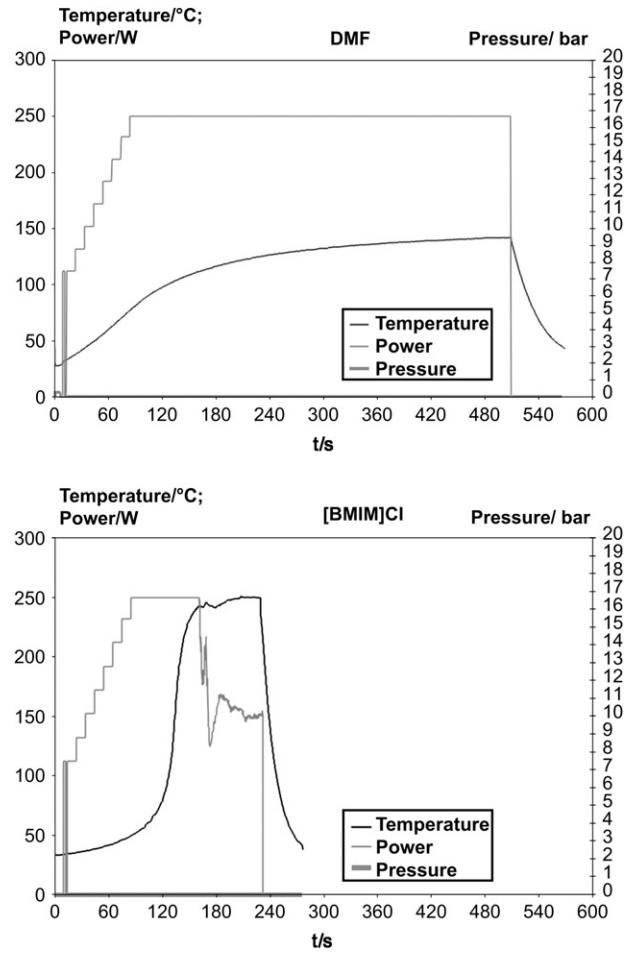


Figure 2. Rates of DMF and [BMIM]Cl microwave heating.

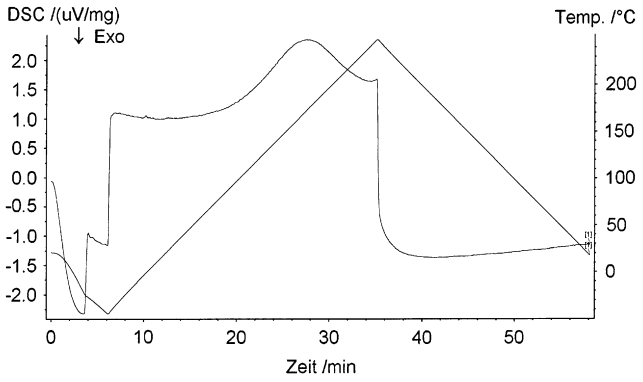


Figure 3. Differential scanning calorimetry of [BMIM]Cl.

therefore, selected for further evaluation. The [BMIM]Cl turned out to be superior again, mainly due to rapid conversion and product purity (Table 1, entries 30–35). Six representative compounds were submitted to a standard protocol: 170 °C for 30 min, 0.5 mmol nitrile, 1.5 mmol NaN_3, 0.5 mmol HOAc. This protocol is similar in reaction time to the Hallberg[9] conditions, but uses a temperature maximum instead of a fixed power input to reduce product decomposition. The yields were superior in five cases, when compared to thermal heating of IL solutions. The yield improvements are less spectacular than reported for microwave heating of DMF solutions.[9] Product **7** (Table 1, entry 31) requires extended reaction time for full conversion, therefore an inadequate 40% yield was observed under these suboptimal conditions.

Finally, the valsartan precursor **8** was synthesized according to literature[4,5] and subjected to tetrazole formation. The adjustment of the NaN_3/HOAc ratio and a gentle thermal heating at 140 °C provided the product in 73% yield at complete conversion (Table 1, entries 23–29). Any extension of the reaction time resulted in slow decomposition of the tetrazole **27**. The microwave heated conversion of this important commercial intermediate **8** resulted in significant improvement of the isolated yield (88%, Table 1, entry 35) and much reduced reaction time (24 h vs 30 min). The upscaling of the reaction, improved the work up procedures such as extraction by CO_2sc and stability of the IL are subject to further investigations.

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